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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,198	11/07/2006	Kumar Visvanathan	DAVI357.001APC	7410

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EXAMINER	
BOESEN, AGNIESZKA	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
10/14/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/550,198	VISVANATHAN ET AL.	
	Examiner	Art Unit	
	AGNIESZKA BOESEN	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81,82,84-88,90-92,137 and 138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81,82,84-88,90-92,137 and 138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/21/2005* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed August 4, 2010 in response to the Office Action of February 4, 2010 is acknowledged and has been entered. Claims 83 and 89 were canceled. Rejections of canceled claims are moot. Claims 81, 86, 87 and 92 have been amended. Claims 81-82, 84-88, 90-92, 137 and 138 are under examination in this Office action.

Claim Objections

Objection to Claim 86 is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 112

Rejection to Claim 92 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** in view of Applicant's amendment.

New rejections in view of Applicant's amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 87-88 and 90-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant amended the claims to recite: "A method for monitoring a response to a therapeutic protocol to treat development of a disease condition (…)". It is not clear what are the metes and bounds of treating the development of a disease condition. Is the disease treated before the disease is really present or the treatment rather refers to treating a disease? Applicant is

suggested to amend the claims to recite "to treat a disease (condition)". The recitation of "condition" is optional. Correction and or clarification is required.

Claims 81, 84 87 and 90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 81, 84 87 and 90 lack a standard for ascertaining the requisite degree of "a change", which would allow one of ordinary skill in the art to be reasonably apprised of the scope of the invention. Second, the claims define "a change" could be either up-regulate or down-regulate, but the claim also require "therapeutic response". It is not clear if up or down-regulating TRL-2/4 is a therapeutic response for treating an infection by a hepatitis virus. Renshaw teaches that the level of TLR2 and TLR-4 changes even in normal cells without infection. One of ordinary skill in the art cannot be reasonably apprised of the metes and bounds of the invention because it is not clear what "change" of TRL-2/4 is intended for "therapeutic response". This rejection affects all dependent claims. Correction and/or clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of Claims 81-82, 84-88, 90-92, 137 and 138 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is maintained**.

Applicant's arguments have been fully considered but fail to persuade. Applicant amended the claims to recite "treat" instead of prevent, hepatitis virus and Toll-like receptor-2 (TLR-2) and Toll-like receptor-4 (TLR-4). Applicant argues that the rejection should be withdrawn and states that Examiner acknowledged, in the paragraph that bridges pages 6 and 7 of the Office action, that the specification does provide support for a correlation between TLR-2/TLR-4 expression with HBV and HCV infection.

In response to Applicant's arguments the Examiner notes that contrary to Applicant's assertions, Examiner did not acknowledged that both TLR-2 and TLR-4 expression correlates with HBV and HCV infection. In the paragraph that bridges pages 6 and 7 of the Office action Examiner states: "The present specification discloses correlation between HBV and HCV infection and TLR-2 expression." Examiner notes that the specification expressly discloses that while the TLR-2 expression was significantly reduced in chronic HBV patients, the TLR-4 expression did not differ in HBV patients and the control group (Example 2). Example 3 discloses that TLR-4 expression on CD14 peripheral blood monocytes was not significantly different in cirrhotic patients and controls. Additionally, the art teaches that while TLR-2 expression is significantly increased in patients with cirrhosis the TLR-4 expression is not significantly different in those patients (see Riodan et al. Hepatology, 2003, Vol. 37, p. 1154-1164). Thus, Examiner does not agree that Applicant's specification or the art disclose that TLR-4 expression correlates with either HBV or HCV infection.

Examiner additionally notes that Applicant amended the claims to broadly recite hepatitis virus. The genus of hepatitis virus includes hepatitis A, B, C, D and E virus. Neither Applicant's specification nor the art show any correlation between hepatitis A, D and E infection and

expression of TLR-2 or TLR-4. Additionally, independent claim 87 broadly recites any disease condition, while the specification does not disclose any other disease conditions besides liver cirrhosis or HCC (see paragraph 0040]. There are other disease conditions that may result from infection with hepatitis virus, besides liver cirrhosis or HCC.

Applicant's claims are broadly drawn to a method for monitoring a response to a therapeutic protocol to treat infection by hepatitis virus and to treat the development of a disease condition comprising determining the level of TLR-2 and TLR-4. As discussed above and on the record Applicants specification provides written description support for the methods of monitoring a response to a therapeutic protocol to treat infection by hepatitis B and hepatitis C virus and to treat liver cirrhosis and HCC comprising determining the level of TLR-2. Applicant's specification does not provide written description support to practice the claimed methods that extend to the whole genus of hepatitis virus, or TLR-4 presently recited in the claims. Thus in view of the foregoing the rejection is maintained.

Rejection of Claims 81-82, 84-88, 90-92, 137 and 138 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement **is maintained.**

Applicant's arguments have been fully considered but fail to persuade. Applicant amended the claims to recite "treat" instead of prevent, hepatitis virus and Toll-like receptor-2 (TLR-2) and Toll-like receptor-4 (TLR-4). Applicant argues that the rejection should be withdrawn and states that Examiner acknowledged, in the paragraph that bridges pages 6 and 7 of the Office action, that the specification does provide support for a correlation between TLR-2/TLR-4 expression with HBV and HCV infection.

In response to Applicant's arguments the Examiner notes that contrary to Applicant's assertions, Examiner did not acknowledged that both TLR-2 and TLR-4 expression correlates with HBV and HCV infection. In the paragraph that bridges pages 6 and 7 of the Office action Examiner states: "The present specification discloses correlation between HBV and HCV infection and TLR-2 expression." Examiner notes that the specification expressly discloses that while the TLR-2 expression was significantly reduced in chronic HBV patients, the TLR-4 expression did not differ in HBV patients and the control group (Example 2). Example 3 discloses that TLR-4 expression on CD14 peripheral blood monocytes was not significantly different in cirrhotic patients and controls. Additionally, the art teaches that while TLR-2 expression is significantly increased in patients with cirrhosis the TLR-4 expression is not significantly different in those patients (see Riodan et al. Hepatology, 2003, Vol. 37, p. 1154-1164). Thus, Examiner does not agree that Applicant's specification or the art disclose that TLR-4 expression correlates with either HBV or HCV infection.

Examiner additionally notes that Applicant amended the claims to broadly recite hepatitis virus. The genus of hepatitis virus includes hepatitis A, B, C, D and E virus. Neither Applicant's specification nor the art show any correlation between hepatitis A, D and E infection and expression of TLR-2 or TLR-4. Additionally, independent claim 87 broadly recites any disease condition, while the specification does not disclose any other disease conditions besides liver cirrhosis or HCC (see paragraph 0040]. There are other disease conditions that may result from infection with hepatitis virus, besides liver cirrhosis or HCC. There is no evidence in the art that any infection and any disease resulting from hepatitis infection correlates with the change in TLR expression or that any medical therapy can influence the levels of TLR expression. The

skilled artisan would have to conduct an undue amount of experimentation in order to positively conclude that by determining the level of TLR receptors and their homologs one of skill in the art could monitor the response to a therapeutic protocol to prevent infection or disease.

Applicant's claims are broadly drawn to a method for monitoring a response to a therapeutic protocol to treat infection by hepatitis virus and to treat the development of a disease condition comprising determining the level of TLR-2 and TLR-4. As discussed above and on the record Applicants specification provides enabling disclosure for the methods of monitoring a response to a therapeutic protocol to treat infection by hepatitis B and hepatitis C virus and to treat liver cirrhosis and HCC comprising determining the level of TLR-2. Applicant's specification does not provide sufficient enablement to practice the claimed methods that extend to the whole genus of hepatitis virus, or TLR-4 presently recited in the claims. Thus in view of the foregoing the rejection is maintained.

Claim Rejections - 35 USC § 102

Rejection of Claims 81, 83-85, 87, 89-91 under 35 U.S.C. 102(b) as being anticipated by Renshaw et al. (Journal of Immunology, 2002, Vol. 169, p. 4697-4701) **is maintained.**

Applicant's arguments have been fully considered but fail to persuade. Applicant amended the claims to recite "treat" instead of prevent, hepatitis virus and Toll-like receptor-2 (TLR-2) and Toll-like receptor-4 (TLR-4). Applicant argues that there is no disclosure of a correlation between TLR-2/TLR-4 expression with viral infection by hepatits virus, such as HBV or HCV, let alone of a method of monitoring a response to a therapeutic protocol to treat

infection by a hepatitis virus, wherein the level(s) of TLR-2 and/or TLR-4 serve as indicator(s) of the efficacy of the therapeutic protocol to treat infection by hepatitis virus.

In response the Examiner acknowledges Applicant's amendment; however the Examiner notes that the recitation of hepatitis virus in the preamble does not limit the claimed **method steps** to measuring the TLR-2 and TLR-4 in patients infected with hepatitis virus. The only active/positive method step recited in the present claims is determining the level of Toll-like receptors TLR-2 and TLR-4.

It is noted that the recitation of the intended use recited in the preamble of the claimed method is not given patentable weight. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Additionally, it is noted that the "wherein" clause is not considered to further limit the claimed method steps. See Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

Renshaw discloses determining the level of expression of TLR-2 and TLR-4 on splenic macrophages by analyzing the mRNA and protein and discloses that the decline in TLR expression and function correlates with increased susceptibility to infection and poor adaptive immune response (see the entire document, particularly Materials and Methods and Figures 1-3).

Thus because Renshaw discloses the claimed method step Renshaw anticipates the present claims and therefore the rejection is maintained.

Claim Rejections - 35 USC § 103

Rejection of Claims 81-92, 137 and 138 under 35 U.S.C. 103(a) as being unpatentable over Renshaw et al. (Journal of Immunology, 2002, Vol. 169, p. 4697-4701) in view of Akira et al. (Immunology Letters, January 2003, Vol. 85, p. 85-95) **is maintained.**

Applicant's arguments have been fully considered but fail to persuade. Applicant amended the claims to recite "treat" instead of prevent, hepatitis virus and Toll-like receptor-2 (TLR-2) and Toll-like receptor-4 (TLR-4). Applicant argues that based on the combined teachings of Renshaw and Akira et al., one of ordinary skill in the art would know of no reason to develop the presently claimed methods of monitoring a response to a therapeutic protocol to treat infection by a hepatitis virus (or to treat development of a disease condition resulting from infection by a hepatitis virus) comprising determining the level of TLR-2 and TLR-4, wherein the efficacy of the therapeutic response is determined by a change in the level of TLR-2 and/or TLR-4.

In response the Examiner notes that it is the Examiner's position that the only active/positive method step recited in the present claims is determining the level of Toll-like receptors TLR-2 and TLR-4, and the limitation of hepatitis virus recited in the preamble is therefore not limiting the claimed method steps, as discussed above. Even if the recitation of "hepatitis virus" was limiting it would have been *prima facie* obvious to provide a method for monitoring a response to a therapeutic protocol to treat hepatitis B and C infection comprising

determining the level of expression of TLR-2 and TLR-4 receptors and comparing the TLR expression level to the pre-treatment sample and the control sample in view of the teachings of Renshaw and Akira for the following reasons.

Renshaw teaches determining the level of expression of TLR-2 and TLR-4 on splenic macrophages by analyzing the mRNA and protein and discloses that the decline in TLR expression and function correlates with increased susceptibility to infection and poor adaptive immune response (see the entire document, particularly Materials and Methods and Figures 1-3).

Renshaw does not teach comparing the level of TLR expression to the pre-treatment sample and to the control sample. Renshaw does not teach pathogenic agents recited in claims 86 and 92.

Akira teaches various pathogenic ligands recognized by the Toll-like receptors, the pathogens are Klebsiella, Chlamydia, Neisseria, Streptococcus, and viruses in general (see Table 1). Akira teaches that the antiviral and the anti-cancer compound imidazoquinoline used for treatment of HCV, Papilloma and Herpes virus infection activate immune cells via Toll-like receptor 7 (see page 90). Akira teaches that the TLR-4 recognizes RS virus (see Table 1).

It would have been *prima facie* obvious to provide a method for monitoring a response to a therapeutic protocol to treat infection by a hepatitis virus comprising determining the level of expression of TLR-2 and TLR-4 receptors and comparing the TLR expression level to the pre-treatment sample and the control sample, because Akira teaches that the TLR-4 recognizes RS virus (see Table 1) and that the antiviral and the anti-cancer compound imidazoquinoline used for treatment of HCV infection activate immune cells via Toll-like receptor 7 (see page 90).

The Supreme Court provided a number of bases on which a claimed invention may be found obvious. One of them is "obvious to try". In particular, "When there is a design need or market pressure to solve a problem and there are a finite number of identified predictable potential solutions, a person of ordinary skill has good reason to pursue the known potential options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense" (*KSR International Co. v. Teleflex Inc.* (82 U.S.P.Q. 2d1385, 2007).

In the present case, since it has been known in the art that TLR-2 and TLR-4 receptors are involved in innate immunity and recognize viral antigens, it would have been obvious to try and to measure the level of TLR receptors, including TLR-2 and TLR-4 receptors, in patients with infection by a hepatitis virus to monitor a response to a therapeutic protocol.

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus because Renshaw in view of Akira teach the claimed methods, as discussed above the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Rejection of Claim 81-82, 84-88, 90-92, 137 and 138 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 7 and 12 of copending Application No. 11/597,063 **is maintained.**

Applicant request that the rejection is held in abeyance until one of the applications is in condition for allowance.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground of rejections presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AGNIESZKA BOESEN whose telephone number is (571)272-8035. The examiner can normally be reached on 9:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen/
Examiner, Art Unit 1648

/BO PENG/
Primary Examiner, Art Unit 1648